BASE-CATALYZED FORMATION OF SPIRO ADDUCT FROM N-METHYL-N-(2,4,6-TRINITROPHENYL)GLYCINAMIDE, THE SMILES REARRANGEMENT OF THE AMIDE IN METHANOL

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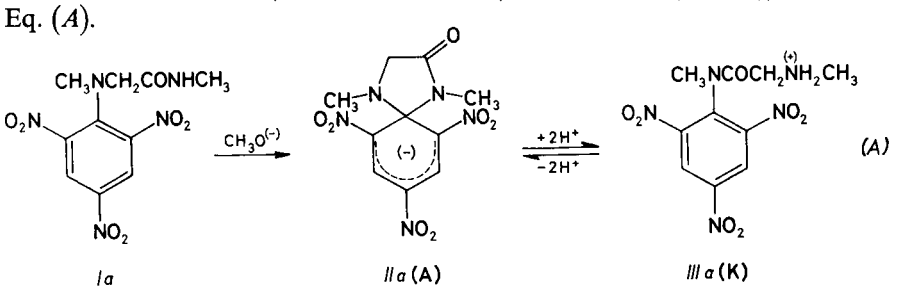
The reaction of N-methyl-N-(2,4,6-trinitrophenyl)glycinamide (*Ic*) with methoxide in methanol produces the spiro adduct *IIc*(A)*. In methanolic acetate buffers, the equilibrium is rapidly established between the spiro adduct *IIc*(A) and the dipolar ion of 2-methylamino-N-(2,4,6-trinitrophenyl)acetamide (*IIIc*(Z)). The equilibrium constant of the reaction *IIIc*(Z) $\rightleftarrows$ *IIc*(A) + H^+ is by eight orders of magnitude greater than that of the analogous cyclization of 2-methylamino-N-methyl-N-(2,4,6-trinitrophenyl)acetamide to the spiro adduct. In chloroacetate buffers, the dipolar ion is protonated to give 2-methylammonium-N-(2,4,6-trinitrophenyl)acetamide *IIIc*(K). The kinetics of the reversible reaction *IIIc*(Z) $\rightleftarrows$ *IIc*(A) + H^+ has been studied in acetate buffers, aliphatic amine – ammonium salt buffers, and methoxide solutions. In all the cases, the rate-limiting step was the proton transfer with half-lives in milliseconds. In more basic methanolic buffers (pH > 10) the rate-limiting step consists in the formation of spiro adduct from the zwitterion *IIIc*(Z) resulting from the protonation of the anion *IIIc*(A). In acetate buffers, the second reaction pathway via the cation *IIIc*(K) is predominant.

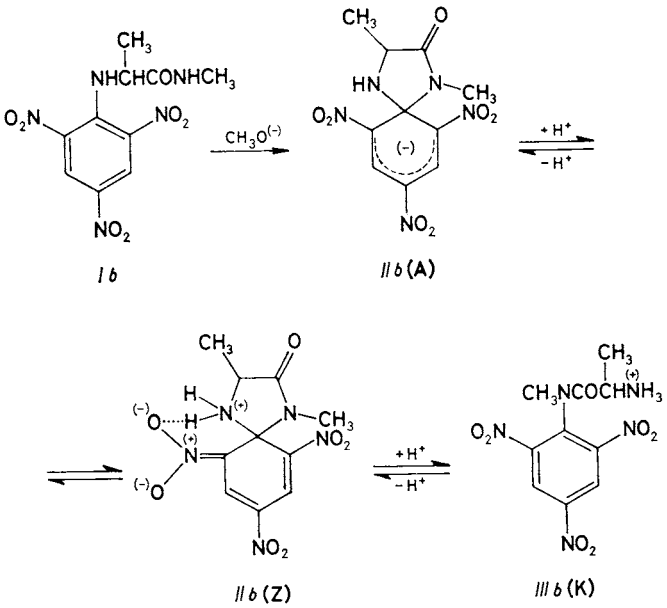
Our previous papers[1,2] dealt with the formation of spiro adducts from N-methyl-N-(2,4,6-trinitrophenyl)glycine methylamide (*Ia*) and N-(2,4,6-trinitrophenyl)alanine methylamide (*Ib*) and the subsequent opening of the spiro adduct giving hydrochlorides of 2-methylamino-N-methyl-N-(2,4,6-trinitrophenyl)acetamide (*IIIa*(K)) and 2-amino-N-methyl-N-(2,4,6-trinitrophenyl)propanamide (*IIIb*(K)), respectively, see Eq. (*A*).



Ia *IIa*(A) *IIIa*(K)

* Some of the compounds dealt with in the present paper exist in two or more acid-base forms. In order to make the text clearer, we add (in brackets) the charge type to each compound number, viz. (K) cation, (A) anion, (Z) zwitterion, (0) without charge.

The equilibrium between the spiro adduct *IIa*(A) and the protonated product of the Smiles rearrangement *IIIa*(K) was studied[1] in aniline–anilinium chloride buffers. In the case of N-(2,4,6-trinitrophenyl)alanine methylamide *Ib*, the equilibrium between the negatively charged spiro adduct *IIb*(A) and the spiro adduct zwitterion *IIb*(Z) is established in the aniline–anilinium chloride buffers, whereas in 4-bromoaniline-4-bromoanilinium chloride buffers the equilibrium is established between the zwitterion *IIb*(Z) and the protonated product *IIIb*(K) of the Smiles rearrangement (Scheme 1). The equilibrium mixtures of *IIa*(A) and *IIb*(A) with the rearrangement products *IIIa*(K) and *IIIb*(K), respectively, never contained spectroscopically detectable amounts of the neutral rearrangement products *IIIa*(0) and *IIIb*(0), respectively, which is obviously due to great cyclization ability of these compounds.



SCHEME 1

In the case of N-methyl-N-(2,4,6-trinitrophenyl)glycinamide *Ic*, the neutral product *IIIc*(0) of the Smiles rearrangement can be stabilized via the proton migration giving the zwitterion *IIIc*(Z) which is unable of cyclization (see Eq. (*B*) where Pi = 2,4,6-trinitrophenyl).

$$\underset{IIIc(O)}{PiNHCOCH_2NHCH_3} \rightleftharpoons \underset{IIIc(Z)}{Pi\overset{(-)}{N}COCH_2\overset{(+)}{N}H_2CH_3} \qquad (B)$$

In addition to it, the rearrangement product *IIIc* lacks (as compared with the compounds *IIIa*(K) and *IIIb*(K)) the methyl group at the nitrogen atom of trinitrophenylamino group, the sterical effect of this methyl group being very favourable for the reverse cyclization to the spiro adduct.

The aim of this work is to find the extent to which these factors affect the equilibrium between the spiro adduct *IIc*(A) and the Smiles rearrangement product and investigate the kinetics of the reactions taking place.

EXPERIMENTAL

The ^{13}C *and* ^{1}H NMR *spectra* were measured at 25·047 and 99·602 MHz, respectively, with a JNM FX-100 (JEOL) spectrometer. The samples used for the measurements were about 10% solutions of the compounds in hexadeuteriodimethyl sulphoxide. The $\delta(^{13}C)$ chemical shifts are related to the middle signal of the solvent multiplet (δ 39·6), the $\delta(^{1}H)$ chemical shifts are related to hexamethyldisiloxane (δ 0·05).

N-*Methyl*-N-(2,4,6-*trinitrophenyl*)*glycinamide* (Ic) was prepared from 1-chloro-2,4,6-trinitrobenzene and N-methylglycinamide hydrochloride by the procedure described for N-methyl-N-(2,4,6-trinitrophenyl)glycine methylamide[1]. Yield 83%, m.p. 145—147°C (ethyl acetate). For $C_9H_9N_5O_7$ (299·2) calculated: 36·13% C, 3·03% H, 23·41% N; found: 36·31% C, 3·31% H, 23·21% N. ^{1}H NMR (hexadeuteriodimethyl sulphoxide): 8·91 s, 2 H (Pi); 7·31 and 7·40 b, 2 H (NH_2); 3·72 s, 2 H (CH_2); 2·96 s, 3 H (NCH_3). ^{13}C NMR (hexadeuteriodimethyl sulphoxide): 166·38 (CO), 143·09 (C-1), 143·38 (C-2,6), 125·54 (C-3,5), 137·94 (C-4), 57·38 (CH_2), 41·71 (NCH_3).

The sodium salt of spiro adduct IIc(A) was prepared by the procedure described[1,2] for the spiro adducts *IIa*(A) and *IIb*(A). Yield 96%; the substance is gradually decomposed on heating. ^{1}H NMR (hexadeuteriodimethyl sulphoxide): 8·55 s, 2 H (Ar); 3·34 s, 2 H (CH_2); 3·7 b, 1 H (NH); 2·20 s, 3 H (NCH_3). ^{13}C NMR (hexadeuteriodimethyl sulphoxide): 172·87 (CO), 78·45 (C-1), 131·62 (C-2,6), 126·54 (C-3,5), 118·05 (C-4), 57·05 (CH_2), 34·22 (CH_3).

2-*Methylamino*-N-(2,4,6-*trinitrophenyl*)*acetamide hydrochloride* IIIc(K) was prepared by the procedure described[1] for 2-methylamino-N-methyl-N-(2,4,6-trinitrophenyl)acetamide. Yield 63% after recrystallization from ethanol with addition of methanolic HCl. The compound undergoes slow cyclization on heating. For $C_9H_{10}ClN_5O_7$ (335·7) calculated: 32·20% C, 3·00% H, 10·56% Cl, 20·87% N; found: 32·43% C, 3·20% H, 10·84% Cl, 20·87% N. ^{1}H NMR (hexadeuteriodimethyl sulphoxide): 9·06 s, 2 H (Pi); 9·7 b, 1 H (NH); 4·10 s, 2 H (CH_2); 2·63 s, 3 H (NCH_3). ^{13}C NMR (hexadeuteriodimethyl sulphoxide): 165·85 (CO), 144·14 (C-1), 145·08 (C-2,6), 124·78 (C-3,5), 128·70 (C-4), 49·49 (CH_2), 32·87 (CH_3).

The measurements of kinetics and equilibria were carried out at 25°C.

a) The equilibrium *IIc*(A) $\rightleftharpoons$ *IIIc*(0) + *IIIc*(Z) was measured by means of a Specord (Zeiss) spectrophotometer in acetate buffers $[CH_3COONa]/[CH_3COOH] = 4$ to 0·25, $[CH_3COONa] = I = 0·04$. A solution of *IIc*(A) (0·4 ml $2·5 \cdot 10^{-4}$ mol l^{-1}) was added to 1·6 ml acetate buffer, and the spectra were measured in the region of 330 to 630 nm. The equilibrium constant was calculated from the absorbances at 500 nm.

b) The equilibrium *IIIc*(K) $\rightleftharpoons$ *IIIc*(0) + H^+ was measured in the same way in chloroacetate buffers $[ClCH_2COOH]/[ClCH_2COONa] = 4$ to 0·125, $[ClCH_2COONa] = I = 0·04$, at $\lambda =$ = 384 nm (the isosbestic point of *IIc*(A) and *IIIc*(Z)).

c) Kinetics of the reaction $Ic \rightarrow IIc$(A) was followed on the Specord (Zeiss) spectrophotometer. A methanolic solution of *Ic* (20 μl $7 \cdot 10^{-3}$ mol l^{-1}) was added to 2 ml methoxide solution ($7 \cdot 10^{-4}$ to $3 \cdot 10^{-3}$ mol l^{-1}), and the absorbance increase was measured at 500 nm. The rate constants were calculated from the relation $kt = -2{\cdot}3 \log (A_\infty - A_t) + \text{const}$.

d) The rate constants of the reversible reaction $IIc(A) \rightleftharpoons IIIc(Z) + IIIc(0)$ were determined with a stopped-flow spectrophotometer Durrum D-110. The reaction was realized by mixing equal volumes of methanolic *IIc*(A) or *IIIc*(K) ($6 \cdot 10^{-5}$ to $2 \cdot 10^{-4}$ mol l^{-1}) and methanolic buffer or methoxide ($2 \cdot 10^{-3}$ to $1{\cdot}6 \cdot 10^{-2}$ mol l^{-1}). The following 1 : 1 mixtures were used as the buffers: 1-butylamine-1-butylammonium chloride, piperidine–piperidinium chloride, triethylamine–triethylammonium chloride (the concentration of base from $2 \cdot 10^{-3}$ to $8 \cdot 10^{-2}$ mol l^{-1}); also used were piperidine–piperidinium chloride 4 : 1, $[C_5H_{11}N] = 1 \cdot 10^{-3}$ to $4 \cdot 10^{-2}$ mol l^{-1}, acetate buffers $[CH_3COOH]/[CH_3COONa] = 4, 3, 2, 1, 0{\cdot}5, 0{\cdot}25, 0{\cdot}125$. In the buffers with $[CH_3COONa] > [CH_3COOH]$ it was $[CH_3COONa] = 3 \cdot 10^{-4}$ to $8 \cdot 10^{-2}$ mol l^{-1}, whereas in the buffers with $[CH_3COONa] < [CH_3COOH]$, where the reactions are very fast, the maximum acetate concentration was lowered down to $[CH_3COONa] = 4 \cdot 10^{-3}$ mol l^{-1}. At higher buffer concentrations, the rate constant could not be reliably determined. A series of measurements was carried out in 1 : 1 triethylamine–triethylammonium chloride buffers ($[(C_2H_5)_3N] = 1 \cdot 10^{-2}$ and $3 \cdot 10^{-2}$ mol l^{-1}) with gradual addition of sodium acetate solution to make its concentration in the buffer equal to $0-6 \cdot 10^{-2}$ mol l^{-1}, as well as in the acetate buffer $[CH_3COONa]/[CH_3COOH] = 100$, $[CH_3COONa] = 8 \cdot 10^{-3}$ to $5 \cdot 10^{-2}$ mol l^{-1}. In all the buffers the ionic strength was adjusted at $I = 0{\cdot}08$ mol l^{-1} by addition of methanolic NaCl.

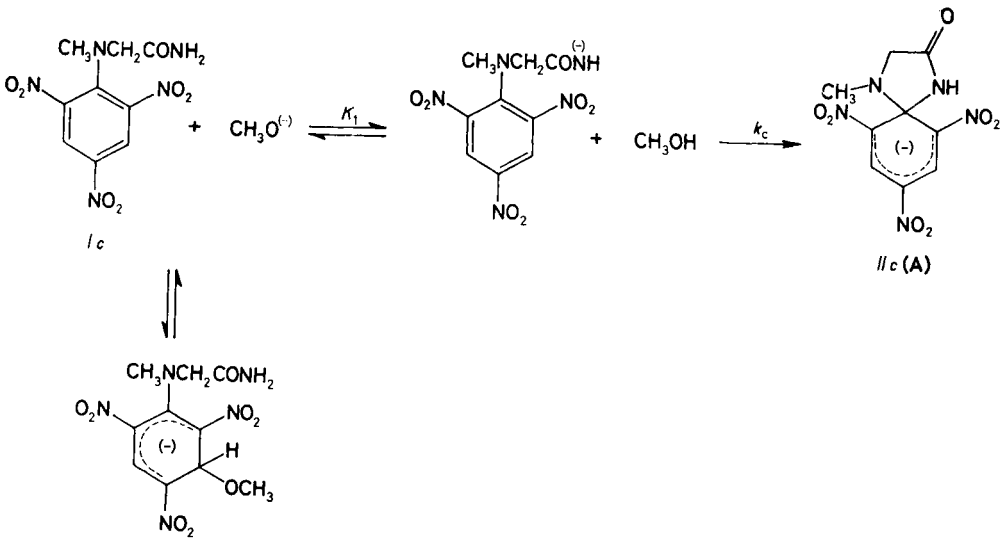
The spiro adduct IIc(A) *stock solution* was prepared by addition of 0·5 ml 0·1 mol l^{-1} methoxide to 10 ml $2 \cdot 10^{-3}$ mol l^{-1} methanolic *Ic* and completing the required volume after c. 15 min. The stock solution of $1 \cdot 10^{-4}$ mol l^{-1} *IIIc*(K) was prepared by dissolving 2-methylamino-N-(2,4,6-trinitrophenyl)acetamide hydrochloride in 10^{-4} mol l^{-1} methanolic HCl. Both the solutions were further diluted if necessary.

When using the methoxide solutions and butylamine, piperidine, triethylamine and acetate buffers with $[CH_3COONa]/[CH_3COOH] = 100$ to 0·5 for the measurements, we followed the establishing of the equilibrium starting from compound *IIIc*(K), whereas for $[CH_3COONa]/[CH_3COOH] \leq 1$ the equilibrium was established from the side of compound *IIc*(A). Hence, in two acetate buffers the equilibrium was followed from both sides.

The measurements were carried out at $\lambda = 500$ nm. The dependence of absorbance vs time was transferred from the memory of a PM 3 311 (Philips) oscilloscope to a BAK 5T (ZPA Čakovice) recorder, and the rate constants were calculated in the standard way.

RESULTS AND DISCUSSION

The reaction of N-methyl-N-(2,4,6-trinitrophenyl)glycinamide *Ic* with methanolic methoxide gives the spiro adduct *IIc*(A) which was isolated and identified by its ^1H and ^{13}C NMR spectra. On addition of methanolic HCl, the spiro adduct is converted practically immediately into the colourless hydrochloride of 2-methylamino-N-(2,4,6-trinitrophenyl)acetamide *IIIc*(K) which was isolated and identified, too. The formation of the spiro adduct *IIc* (A) is described in Scheme 2. The reactions taking place were followed spectroscopically at $[CH_3O^-] = 4 \cdot 10^{-4}$ to $3 \cdot 10^{-3}$ mol.



SCHEME 2

. l^{-1}. Under these conditions, the concentrations of both the conjugated base of compound *Ic* and the 1,3-adduct* can be neglected (as compared with the concentration of compound *Ic*), hence the dependence of experimental rate constant k_{exp} on $[CH_3O^-]$ is linear (Eq. (*1*)).

$$k_{exp} = k_2[CH_3O^-] \qquad (1)$$

The bimolecular rate constant $k_2 = K_1 k_c = 12\ l\ mol^{-1}\ s^{-1}$ is about fifteen times smaller than that of the cyclization of N-methyl-N-(2,4,6-trinitrophenyl) glycinemethylamide ($k_2 = 175\ l\ mol^{-1}\ s^{-1}$, ref.[1]). This means that the replacement of hydrogen atom of the amidic group by a methyl group causes acceleration of the base-catalyzed cyclization by about one order of magnitude. A similar acceleration was observed earlier in base-catalyzed cyclizations giving five-membered[5,6] and six-membered cycles[7].

Transformation of Spiro Adduct IIc(A) *into the Smiles Rearrangement Products*

An addition of 20 μl methanolic acetate buffer ($[CH_3COOH]/[CH_3COONa] = 1$, $[CH_3COONa] = 2 . 10^{-2}\ mol\ l^{-1}$) to 2 ml solution of $3{\cdot}36 . 10^{-5}\ mol\ l^{-1}$ spiro adduct *IIc*(A) in about $10^{-3}\ mol\ l^{-1}$ methoxide brings about an immediate absor-

* According to refs[3,4], the equilibrium constants of formation of the 1,3-adducts of N-alkylpicramides with methoxide have the values of 10—20.

bance decrease at $\lambda > 384$ nm and an absorbance increase at $\lambda < 384$ nm (Fig. 1). Addition of further 20 µl acetate buffer ($[CH_3COOH]/[CH_3COONa] = 6$, $[CH_3COONa] = 2 \cdot 10^{-2}$ mol l^{-1}, the resultant buffer components ratio $[CH_3COONa]/[CH_3COOH] \approx 0{\cdot}4$) causes another immediate spectral change in the same direction as above, and the spectrum obtained approaches in its character that of the starting compound *Ic* (Fig. 1, the spectra *4* and *5*). The presence of the starting compound was excluded by the fact that a subsequent acidification of the mixture with 20 µl 3 mol l^{-1} methanolic HCl makes the spectrum identical with that of compound *IIIc*(K) (which was prepared on preparative scale). On the other hand, an addition of excess acetate to the mixture exhibiting the spectrum *4* (Fig. 1) again produces the spiro adduct *IIc*(A). The spectra of the starting compound *Ic* in methanolic acetate buffers and in methanolic HCl are identical. The only possible explanation of the observation described is that in acetate buffers equilibrium is established between the spiro adduct *IIc*(A) and the neutral 2-methylamino-N-(2,4,6-trinitrophenyl)acetamide *IIIc*(0) which is predominantly present in the form of the zwitterion *IIIc*(Z) in methanolic solutions (Eq. (*C*)). With increasing H^+ concentration, equilibrium is established between the zwitterion *IIIc*(Z) and the protonated compound *IIIc*(K). (Eq. (*D*)).

$$IIc(\mathrm{A}) + H^+ \overset{K_2}{\rightleftharpoons} \mathrm{PiNHCOCH_2NHCH_3} \longrightarrow \overset{(-)}{\mathrm{Pi}}\mathrm{N}\overset{(+)}{\mathrm{C}}\mathrm{OCH_2NH_2CH_3} \quad (C)$$

$$\overset{(-)}{\mathrm{Pi}}\mathrm{N}\overset{(+)}{\mathrm{C}}\mathrm{OCH_2NH_2CH_3} + H^+ \overset{K_A}{\rightleftharpoons} \mathrm{PiNHCO}\overset{(+)}{\mathrm{C}}\mathrm{H_2NH_2CH_3} \quad (D)$$

This reaction mechanism was confirmed by the measurements of the equilibrium

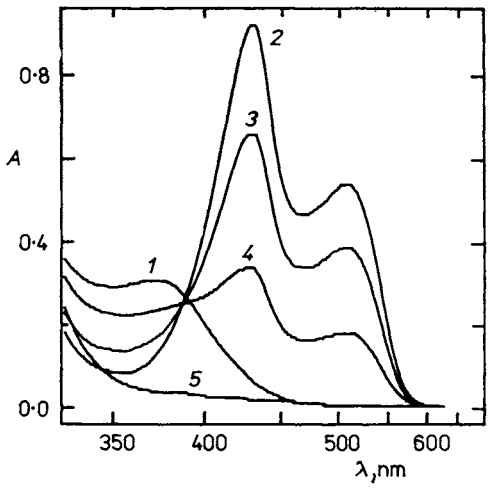


FIG. 1

The electronic spectra of N-methyl-N-(2,4,6-trinitrophenyl)glycinamide *Ic* in methanol (spectrum *1*), spiro adduct *IIc*(A) in 10^{-3} mol l^{-1} CH_3ONa (spectrum *2*), the mixture after addition of 20 µl acetate buffer ($[CH_3COOH]/[CH_3COONa] = 1$, $[CH_3COONa] = 2 \cdot 10^{-2}$ mol l^{-1}, spectrum *3*), after further addition of 20 µl acetate buffer ($[CH_3COOH]/[CH_3COONa] = 6$, $[CH_3COONa] = 2 \cdot 10^{-2}$ mol l^{-1}, spectrum *4*), and compound *IIIa*(K) in $3 \cdot 10^{-2}$ mol l^{-1} methanolic HCl (spectrum *5*); the concentration of the compound was always $3{\cdot}36 \cdot 10^{-5}$ mol l^{-1}

constants between the spiro adduct and compounds *IIIc*(0) + *IIIc*(Z) in acetate buffers and those of the dissociation constant of *IIIc*(K) to *IIIc*(Z) in chloroacetate buffers.

$$K_{A2} = \frac{[IIc(A)]\,[H^+]}{[IIIc(Z)]} = \frac{A[H^+]}{A^{II} - A}\left(1 + \frac{[H^+]}{K_A}\right) = R[H^+] \qquad (2)$$

The equilibrium constant K_{A2} is defined by the relation (*2*), where A means the absorbance of the compound mixture *IIc*(A), *IIIc*(Z), and *IIIc*(K) measured at 500 nm, and A^{II} means the absorbance of the spiro adduct *IIc*(A) alone measured at the same wavelength and concentration. The absorbance A is proportional to the concentration of spiro adduct *IIc*(A) in the equilibrium mixture, the difference $(A^{II} - A)$ being proportional to the sum of concentrations of *IIIc*(K) + *IIIc*(Z). The expression $(1 + [H^+]/K_A)^{-1}$ corresponds to the share of *IIIc*(Z) in the mixture of *IIIc*(Z) and *IIIc*(K), and it makes itself felt in the most acidic acetate buffers in which *IIIc*(K) is present beside *IIIc*(Z). Negative logarithm of the equilibrium constant K_{A2} was calculated from Eq. (*3*) where the value 9·52 corresponds to pK_A of acetic acid in methanol[8], 0·25 represents the correction for ionic strength[8,9], and 0·02 is the ΔpK_A found from the dependence of log R (Eq. (*2*)) on log ($[CH_3COONa]/[CH_3COOH]$).

$$pK_{A2} = 9{\cdot}52 - 0{\cdot}25 - 0{\cdot}02 = 9{\cdot}25 \pm 0{\cdot}03 \qquad (3)$$

$$K_{A3} = \frac{[IIIc(Z)]\,[H^+]}{[IIIc(K)]} = \frac{A - A^K}{A^Z - A}\left(\frac{[H^+]}{K_2 + [H^+]}\right) \qquad (4)$$

The dissociation constant of compound *IIIc*(K) was determined in similar way from Eq. (*4*), where A^Z is the absorbance of zwitterion *IIIc*(Z) measured in the isosbestic point 384 nm of its spectrum with that of *IIc*(A); A^K stands for the absorbance of compound *IIIc*(K). The expression in the numerator is proportional to the concentration sum $[IIIc(Z)] + [IIc(A)]$, that in the denominator is proportional to $[IIIc(K)]$, and the expression in the brackets represents the share of *IIIc*(Z) in its equilibrium mixture with the spiro adduct *IIc*(A) and makes itself felt in the most basic chloroacetate buffers. The pK_{A3} value of compound *IIIc*(K) was calculated from Eq. (*5*), where 7·96 represents the pK_A value of chloroacetic acid in methanol[8], 0·25 is the correction for ionic strength, and $\Delta pK_A = 0{\cdot}30$

$$pK_{A3} = 7{\cdot}96 - 0{\cdot}25 + 0{\cdot}30 = 8{\cdot}01 \pm 0{\cdot}05\,. \qquad (5)$$

The behaviour of spiro adduct *IIc*(A) in its relation to the Smiles rearrangement products is different from that of the spiro adducts studied earlier, especially of *IIa*(A).

In the transformation of spiro adduct *IIa*(A) into the rearrangement product *IIIa*(K), the concentration of the neutral form *IIIa*(0) of the rearrangement product is negligibly low over the whole pH range studied (the zwitterion type *IIIc*(Z) cannot be formed). Hence, the pH dependence of the absorbance ratio coresponding to the [*IIa*(A)]/[*IIIa*(K)] ratio is linear with the slope 2 (ref.[1]), whereas in the case of spiro adduct *IIc*(A) the transformation into the rearrangement product *IIIc*(K) proceeds in two separated steps. The concentration ratio of the neutral and positively charged forms of the rearrangement product is given by Eq. (*6*)

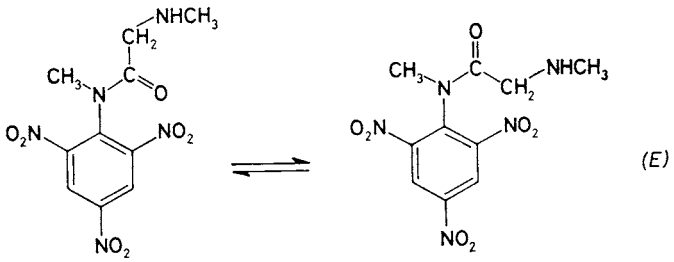
$$[IIIc(K)] : ([IIIc(Z)] + [IIIc(0)]) : [IIc(A)] = \\ = 1 : (K_{A3}/[H^+]) : (K_{A2}K_{A3}/[H^+]^2) . \qquad (6)$$

This means that the compounds *IIIc*(K) and *IIc*(A) are present in the equilibrium mixture in the ratio of 1 : 1 at pH = $(pK_{A2} + pK_{A3})/2 = 8{\cdot}63$. At this pH value, the compounds of Eq. (*6*) are in the ratio of 1 : 4·2 : 1. Hence, the concentration equality [*IIc*(A)] = [*IIIc*(K)] is attained at an H^+ concentration by three orders lower than in the case of compounds *IIa*(A) and (*Z-IIIa*(K) + *E-IIIa*(K)) which stand in the ratio 1 : 1 at pH 5·53 (ref.[1]). The ratio [*Z-IIIa*(K)]/[*E-IIIa*(K)] = 2·5, hence the equal concentrations [*IIa*(A)] = [*Z-IIIa*(K)] are reached at pH 5·38. From the $pK_A = 9{\cdot}27$ determined for the compound *Z-IIIa*(K) from kinetic measurements[1] it can be calculated that the ratio is [*Z-IIIa*(0)]/[*IIa*(A)] = $1{\cdot}25 \cdot 10^{-4}$ at pH 5·35, hence at pH 9·27 (when the concentrations are [*Z-IIIc*(Z)] = [*IIc*(A)] = 1) the compounds *Z-IIIa*(0) and *IIa*(A) are present in the ratio of $1{\cdot}6 \cdot 10^{-8}$: 1.

Thus the stability ratio of the spiro adduct *IIa*(A) to the neutral rearrangement product *Z-IIIa*(0) is by about 8 orders of magnitude greater than the stability ratio of the spiro adduct *IIc*(A) to the zwitterion *Z-IIIc*(Z). The cyclization of the *Z*-forms of the rearrangement products proceeds in two steps[1]: in the first step the *Z*-form is isomerized to the *E*-form, in the second step the *E*-form is cyclized to the spiro adduct. The difference of almost eight orders in the relative stabilities of the spiro adducts *II* and the non-cyclizing *Z*-forms of the rearrangement product *III* (uncharged for *IIIa* and predominantly zwitterion for *IIIc*) is divided into both reaction steps of the cyclization. It is presumed that the ratio [*Z-III*]/[*E-III*] is by about 3–5 orders greater and the ratio [*E-III*]/[*II*] is by about 3–5 orders lower in the case of *E-IIIc*(Z) than in the case of *E-IIIa*(0). The greater stability of the spiro adduct *IIa*(A), as compared with the spiro adduct *IIc*(A), can be explained by the effect of methyl group at the picramide nitrogen atom in the case of *IIa*(A). Alkyl groups are known to generally shift the cyclization equilibria in favour of the cyclized compounds[10].

The second factor which affects the relative stability of spiro adducts and neutral products of the Smiles rearrangement is the share of the cyclizing *E-III*(0) form in its

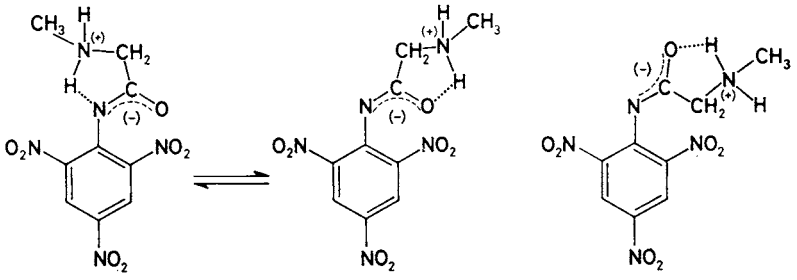
mixture with the other isomers of compound *III*. In the case of *Z-IIIa*(0), the methyl group at picramide nitrogen atom lowers (by its sterical interactions) the stability of the non-cyclizing *Z*-form (Eq. (*E*)).



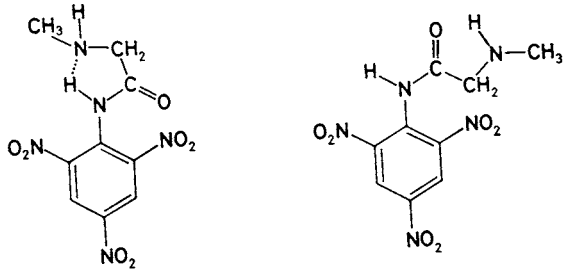
(*E*)

Z-*III a* (0) *E*-*III a* (0)

The cyclizing compound *E-IIIc*(0) is in equilibrium with the non-cyclizable forms (Eq. (*F*)). In contrast to the cyclizing *E-IIIa*(0) form, both the *Z* and *E* isomers of compound *IIIc* predominantly exist in the form of non-cyclizable zwitterions. All the forms at the left-hand side of Eq. (*F*) are stabilized by intramolecular hydrogen



Z-*III c* (Z) *E*-*III c* (Z)



Z-*III c* (0) *E*-*III c* (0)

bonds and, in addition to it, they have no methyl group at the picramide nitrogen atom (the methyl group in compound *Z-IIIa*(0) favours the cyclizable *E*-form). All the factors given favour the non-cyclizable forms of compound *IIIc* to the detriment of the cyclizing form *E-IIIc*(0).

$$Z\text{-}IIIc(Z) + Z\text{-}IIIc(0) + E\text{-}IIIc(Z) \rightleftharpoons E\text{-}IIIc(0) \qquad (F)$$

Kinetics of the Reversible Reaction IIc(A) + HA ⇌ IIIc(Z) + IIIc(0) + A^-

The transformation kinetics of compound *IIIc* into spiro adduct *IIc*(A) was studied in methoxide solutions and in 1-butylamine, piperidine, and triethylamine buffers. In methoxide and in butylamine and piperidine buffers, the formation of the spiro adduct is quantitative, whereas in the triethylamine buffers it leads to an equilibrium in which about 2–3% of compound *IIIc*(Z) is present beside the spiro adduct. The observed rate constants k_{obs} increase linearly with methoxide or buffer concentration, being practically independent of the buffer component ratio. The observed rate constant k_{obs} is defined by Eq. (7)

$$k_{obs} = k_0 + k_B[B], \qquad (7)$$

where B means the basic buffer component or methoxide. The k_0 constant significantly differs from zero in the triethylamine buffers only. Table I presents the rate constant values found.

TABLE I

The rate constants of reversible reaction *IIc*(A) ⇄ *IIIc*(Z) + *IIIc*(O) in methoxide solutions and methanolic buffers

Buffer	k, l mol^{-1} s^{-1}	pK_A
$CH_3O^{(-)}$	$(4{\cdot}6 \pm 0{\cdot}4) \cdot 10^4$	18·4
$C_4H_9NH_2 + C_4H_9NH_3Cl$	$(8{\cdot}4 \pm 0{\cdot}6) \cdot 10^3$	11·7 (ref.[11])
$C_5H_{10}N + C_5H_{10}NHCl(1:1)$	$(7{\cdot}8 \pm 0{\cdot}3) \cdot 10^3$	11·8 (ref.[12])
$C_5H_{10}N + C_5H_{10}NHCl(4:1)$	$(8{\cdot}5 \pm 0{\cdot}2) \cdot 10^3$	—
$(C_2H_5)_3N + (C_2H_5)_3NHCl$	$(1{\cdot}6 \pm 0{\cdot}1) \cdot 10^3$	10·88 (ref.[13])
$CH_3COONa + CH_3COOH$	$(4{\cdot}5 \pm 0{\cdot}8) \cdot 10^{4a}$	9·52 (ref.[8])
	$(1{\cdot}1 \pm 0{\cdot}1) \cdot 10^{3a}$	—
CH_3OH	$k_0 = 4 \pm 1\ s^{-1}$	

[a] The parameters *a* and *d* from Eq. (*10*).

The rate of establishing of the equilibrium *IIIc*(Z) ⇌ *IIc*(A) + H^+ was studied in acetate buffers. The establishing of the equilibrium in the directions → and ← was followed in the buffers with the component ratio $[CH_3COONa]/[CH_3COOH] = 6$ to 0·5 and 1 to 0·25, respectively. The observed rate constants k_{obs} increase linearly with the buffer concentration and in the buffers with the component ratios 1 : 1 and 1 : 2, the same k_{obs} values were obtained for the same buffer concentrations when following the reaction in both directions. The linear dependences on the buffer concentration extrapolated to zero buffer concentration gave non-zero intercepts at the *y* axis, their values being increased with decreasing $[CH_3COONa]/[CH_3COOH]$ ratio. For the buffer component ratio of 0·25 the intercept has the value $(10 \pm 4)\ s^{-1}$.

The kinetics of formation of spiro adduct *IIc*(A) was also studied in acetate buffers with the component ratio $[CH_3COONa]/[CH_3COOH] = 100$ and in two triethylamine buffers with gradual addition of acetate. In these cases the dependences on the acetate concentration were not linear, the initial increase being steepest at higher triethylamine concentration (Fig. 2).

Findings Obtained from Kinetic Measurements

The reversible reactions *IIa*(A) + 2 H^+ ⇌ *IIIa*(K) and *IIb*(A) + 2 H^+ ⇌ *IIIb*(K) proceed kinetically in two steps[1,2]: the fast cyclization of the *E*-form is followed by the slow isomerization *Z-III*(K) → *E-III*(K) (the half-lives in seconds). The cyclization rate *E-III*(0) → *II*(A) + H^+ is much too high to be measured. The reversible reaction *Z-IIIc*(Z) ⇌ *IIc*(A) proceeded in all the cases in a single step with half-lives in milliseconds. Hence, the isomerization *Z-IIIc*(Z) ⇌ *E-IIIc*(Z) must be, in this case, by several orders faster than that of compounds *Z-IIIa*(K), *Z-IIIa*(0), *Z-IIIb*(K), and *Z-IIIb*(0). An acceptable explanation is that the isomerization *Z-IIIc*(Z) ⇌

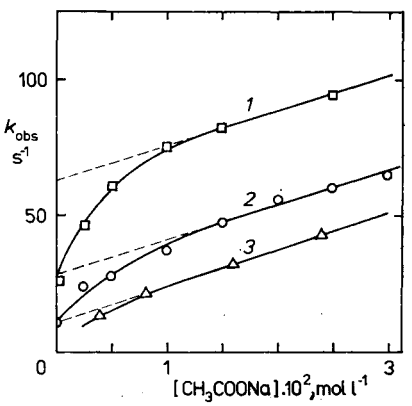


FIG. 2

The dependence of the rate constant k_{obs} of formation of spiro adduct *IIc*(A) on the sodium acetate concentration in triethylamine–triethylammonium chloride buffers (1 : 1) with the concentrations $[(C_2H_5)_3N] = 1{\cdot}5 \cdot 10^{-2}$ mol l^{-1} (*1*), $5 \cdot 10^{-3}$ mol l^{-1} (*2*), and without the buffer (*3*)

$\rightleftharpoons$ *E-IIIc*(Z) is not realized by the rotation around the partially double bond C=N, in contrast to the other isomerizations studied[1,2] which involved a methyl group at the picramide nitrogen atom, but proceeds by the inversion at nitrogen atom in the dipolar ion *IIIc*(Z) or anion *IIIc*(A) ($PiN^{(-)}COCH_2NHCH_3$). In all the buffers used, the transformation *IIIc*(Z) $\rightleftharpoons$ *IIc*(A) proceeded as a generally base- and a generally acid-catalyzed reactions in the directions $\rightarrow$ and $\leftarrow$, respectively, which means that the rate-limiting step always consisted in the proton transfer and not in the cyclization, ring opening of spiro adduct, or the isomerization itself.

The largest body of information about the mechanism of the reaction *IIIc*(Z) $\rightleftharpoons$ $\rightleftharpoons$ *IIc*(A) was provided by the measurements in acetate buffers where the reversible reaction is catalyzed by both the buffer components according to Eq. (*8*)

$$k_f[CH_3COONa]\,[IIIc(Z)] = k_r[CH_3COOH]\,[IIc(A)]\,, \qquad (8)$$

where k_f and k_r mean the reaction rate constants in the directions $\rightarrow$ and $\rightarrow$, respectively. Since in the 1 : 1 acetate buffer the concentration ratio is $[IIIc(Z)]/[IIc(A)] \approx$ ≈ 1 ($\Delta pK_A = 0{\cdot}02$ (Eq. (*3*)) is smaller than the experimental error), it is $k_f \approx k_r \approx k$. Hence, Eq. (*9*) is obtained for the rate constant k_{obs}.*

$$k_{obs} = k_f[CH_3COONa] + k_r[CH_3COOH] =$$
$$= k([CH_3COONa] + [CH_3COOH]) = k[\text{buffer}] \qquad (9)$$

In Fig. 3 there is the pH dependence of log k_{obs} (Eq. (*9*)). At the highest pH values, the rate of the predominant reaction is independent of the proton concentration, with decreasing pH the other reaction pathway gradually becomes significant, and the rate increases with increasing proton concentraion (the increasing positive slope value in Fig. 3). The further pH decrease again causes lowering of the slope in Fig. 3, which means that the rate-limiting step of this second reaction pathway is changed, and the reaction rate again becomes independent of the proton concentration. The mentioned pH dependence of the rate constant is described by the empirical kinetic equation (*10*) (ref.[14])

$$k = a + \frac{b[H^+]}{1 + c[H^+]} = a + \frac{d}{1 + e/[H^+]}\,. \qquad (10)$$

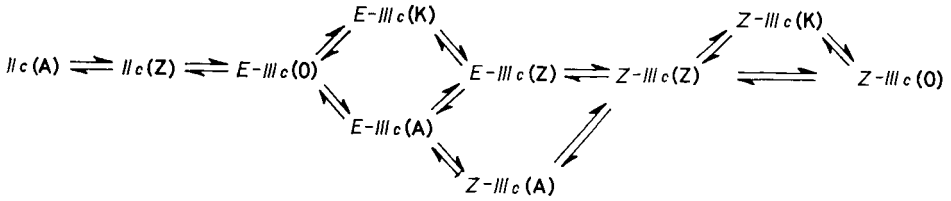
The theoretical dependence in Fig. 3 was calculated from Eq. (*10*) with application of the following parameters: $a = 1{\cdot}1\,.\,10^3\ l\,mol^{-1}\,s^{-1}$, $d = 4{\cdot}5\,.\,10^4\ l\,mol^{-1}\,s^{-1}$,

* More precisely, $k_{obs} = k[\text{buffer}] + k_0$, where k_0 means the rate constant of the reaction catalyzed by methanol and by the proton.

$e = 2{\cdot}2 \cdot 10^{-9}\ \mathrm{l\,mol^{-1}\,s^{-1}}$. At higher concentrations of acid, compound *IIIc*(K) ($pK_{A3} = 8{\cdot}0$) is accumulated in the reaction mixture. Therefore, the rate constant k_{obs} calculated from Eq. (*9*) for acetate buffers with $[CH_3COOH]/[CH_3COONa] \geqq 1$ was corrected by multiplication with the fraction P (Eq. (*11*))

$$P = ([IIIc(Z)] + [IIc(A)])/([IIIc(Z)] + [IIc(A)] + [IIIc(K)])\,. \qquad (11)$$

Conceivable reaction pathways of the reaction *IIIc*(Z) ⇌ *IIc*(A) are given in Scheme 3. The dipolar ion *Z-IIIc*(Z) can be converted into *Z-IIIc*(0) by the proton transfer involving intramolecular hydrogen bond, but *E-IIIc*(0) can only be transformed via the cation *E-IIIc*(K) or anion *E-IIIc*(A). In basic acetate buffers the reaction predominantly goes via the anions *E-IIIc*(A) and/or *Z-IIIc*(A). With increasing proton concentration, the pathway involving the formation of the cation *E-IIIc*(K) as the rate-limiting step becomes more advantageous. At the highest proton concentration (in acetate buffers), the rates of the transformations *E-IIIc*(0) + H^+ → *E-IIIc*(K) and *E-IIIc*(0) → H^+ + *E-IIc*(A) are comparable, and the reversible transformation *IIc*(A) ⇌ *IIc*(Z) gradually becomes rate-limiting.



SCHEME 3

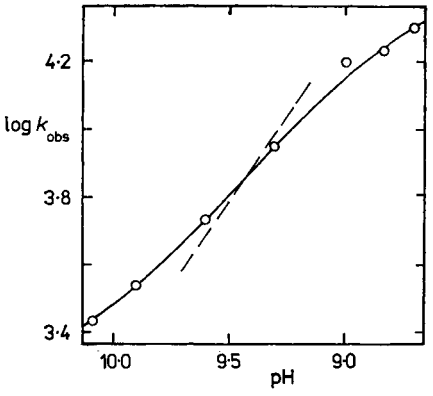
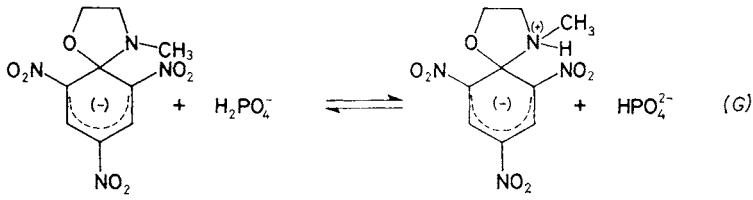


FIG. 3

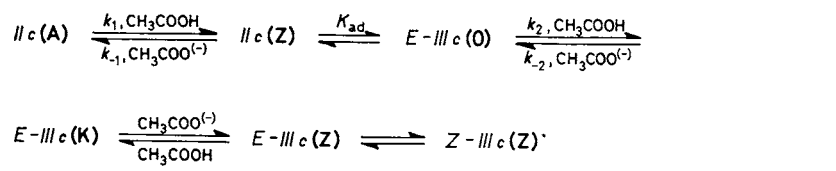
The dependence of logarithm of the rate constant k_{obs} of formation of the equilibrium mixture *IIIc*(Z) + *IIc*(A) on pH in the acetate buffers. The full line was calculated from Eq. (*10*) with application of the correction factor P (Eq. (*11*)) and the parameters $a = 1{\cdot}1 \cdot 10^3\ \mathrm{l\,mol^{-1}\,s^{-1}}$, $d = 4{\cdot}5 \cdot 10^4$ l. . $\mathrm{mol^{-1}\,s^{-1}}$, $e = 2{\cdot}2 \cdot 10^{-9}\ \mathrm{mol\,l^{-1}}$. The dash line has the slope 1

A more accurate picture of the reaction courses in Scheme 3 can be obtained by an attempt at determination of the values of some rate and equilibrium constants on the basis of analogy with the systems studied earlier[1,2]. The empirical kinetic equation (*10*) is reduced, at high proton concentrations, to the simplified form $k = d = 4{\cdot}5 \,.\, 10^4\ \mathrm{l\ mol^{-1}\ s^{-1}}$, k being – under this approximation – the rate constant of the reaction *IIc*(A) + $CH_3COOH \rightleftharpoons$ *IIc*(Z) + $CH_3COO^{(-)}$. As the pK_A values of the dipolar ions type *IIc*(Z) are always substantially smaller than pK_A of acetic acid[1,2], the reverse reaction is thermodynamically advantageous. By analogy with the reaction (*G*) we can presume the approximate value $k = 2 \,.\, 10^8\ \mathrm{l\ mol^{-1}\ s^{-1}}$ for the rate constant of the reverse reaction of the zwitterion *IIc*(Z) + $CH_3COO^{(-)} \rightarrow$ *IIc*(A) + CH_3COOH. Hence for the zwitterion *IIc*(Z) we obtain the value $pK_A = 5{\cdot}6$. For the zwitterion of spiro adduct *IIb*(Z) we found by measurement[2] the value $pK_A = 5{\cdot}85$, and Bernasconi[15] gives the value $pK_A = 5{\cdot}7$ for the zwitterion of the spiro adduct in Eq. (*G*) (in water). From the assessed value pK_A of the zwitterion *IIc*(Z) (5·6) and from the pK_{A2} of the equilibrium *IIc*(A) $\rightleftharpoons$ $\rightleftharpoons$ *IIIc*(Z) (9·25) it follows that the concentration ratio [*IIc*(Z)]/[*IIIc*(Z)] is about $2{\cdot}2 \,.\, 10^{-4}$.



In the case of compound *IIa*(A), the value $pK_{A2} = 9{\cdot}27$ was found for the reaction *Z-IIIa*(K) $\rightleftharpoons$ *Z-IIIa*(0) + H^+ from the kinetic measurements[1]. The equilibrium *E-IIIc*(K) $\rightleftharpoons$ *E-IIIc*(0) + H^+ is presumed to have a similar pK_A value. The pK_A value found experimentally for the reaction *Z-IIIc*(K) $\rightleftharpoons$ *Z-IIIc*(Z) + H^+ is 8·01. This value is lower when compared with the above-mentioned presumed pK_A value ($\approx$9·27), because the zwitterion can be stabilized by two intramolecular hydrogen bonds. The dipolar ion *E-IIIc*(Z) can be stabilized by a single intramolecular hydrogen bond and, therefore, is a somewhat stronger base than *Z-IIIc*(Z), being, however, a far weaker base than *E-IIIc*(0). Therefrom it follows that the reaction of *E-IIIc*(K) with acetate will more rapidly produce the thermodynamically more stable dipolar ion *E-IIIc*(Z) than the uncharged *E-IIIc*(0), hence the rate-limiting step of the acid-catalyzed transformation *IIc*(A) $\rightarrow$ *E-IIIc*(Z) will be the step *E-IIIc*(0) $\rightleftharpoons$ *E-IIIc*(K).

Scheme 4 describes the transformation of the spiro adduct *IIc*(A) into compound *E-IIIc*(Z) via the cation *E-IIIc*(K). The rate-limiting step consists in the reaction of neutral compound *E-IIIc*(0) with acetic acid, hence the rate constant k (Eq. (*9*)) is defined by the relation (*12*),



SCHEME 4

$$k = \frac{k_1[\mathrm{CH_3COOH}]\,K_{ad}k_2}{k_{-1}[\mathrm{CH_3COO^{(-)}}] + K_{ad}k_2[\mathrm{CH_3COO^{(-)}}]} = \frac{d}{1 + e/[\mathrm{H^+}]}, \qquad (12)$$

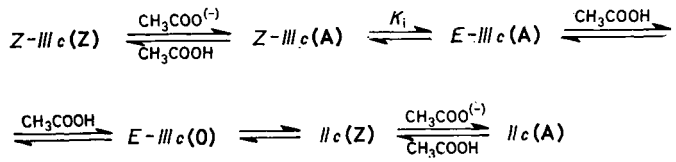
where $d = k_1$ and $e = k_{-1}K_{HA}/k_2K_{ad}$, where K_{HA} is the dissociation constant of acetic acid ($5{\cdot}6 \cdot 10^{-10}$). The form of the kinetic equation (*12*) is, except for the constant, identical with the empirical equation (*10*). According to Eigen[16], the rate constant of the proton transfer between acetic acid and amine with $\Delta pK_A = 0$ has the value of about $3 \cdot 10^8$ l mol^{-1} s^{-1}. On introducing the above-mentioned values of the constants k_{-1}, k_2 (Eq. (*10*)), and K_{HA} into the expression for e (Eq. (*12*)) we obtain the value $K_{ad} = 0{\cdot}15$. From the equilibrium constant K_{ad} and from the above-mentioned ratio $[IIc(Z)]/[IIIc(Z)] = 2{\cdot}2 \cdot 10^{-4}$ it is possible to calculate the ratio $[E\text{-}IIIc(0)]/[Z\text{-}IIIc(Z)] = K_{ad} \cdot 2{\cdot}2 \cdot 10^{-4} = 3{\cdot}3 \cdot 10^{-5}$.

The value given for the ratio $[E\text{-}IIIc(0)]/[Z\text{-}IIIc(Z)]$ depends only on the value of parameter e found from the kinetic data, on the dissociation constant of acetic acid (from ref.[8]), and on the assessed value of the rate constant k_2 (ref.[15]). The error of the estimate of k_{-1} (and, hence, also of the ratio $[IIc(Z)]/[Z\text{-}IIIc(Z)]$) is accompanied by the same error in the estimate of K_{ad}, they cancel each other and have no effect on the magnitude of the $[IIc(Z)]/[Z\text{-}IIIc(Z)]$ ratio. If we would presume the error in the estimate of pK_A of the reaction $Z\text{-}IIIc(Z) \rightleftharpoons Z\text{-}IIIc(0)$ to be ± 1 (i.e. the value $pK_A = 9{\cdot}25 \pm 1$), which is a very pessimistic presumption, then the k_2 rate constant should have the value in the range $(1{\cdot}2$ to $6{\cdot}0) \cdot 10^8$ l mol^{-1} s^{-1}, and the concentration ratio $[IIc(Z)]/[Z\text{-}IIIc(Z)] = (4{\cdot}5 \pm 3) \cdot 10^{-5}$. Hence, the concentration of the zwitterion of spiro adduct $IIc(Z)$ is more than by four orders of magnitude lower than that of zwitterion $Z\text{-}IIIc(Z)$. Therefrom it follows that the replacement of hydrogen atom at the picramide nitrogen of compound *IIIc* by a methyl group (compound *IIIa*) increases the equilibrium constant of the reaction $E\text{-}IIIc(0) \rightleftharpoons IIc(A) + H^+$ by 3·5 orders of magnitude.

In the amine–ammonium chloride buffers used (amine = 1-butylamine, triethylamine, piperidine), in methoxide solutions, and mostly also in basic acetate buffers, the transformation $Z\text{-}IIIc(Z) \rightleftharpoons IIc(A)$ goes through a negative intermediate or intermediates (Scheme 3). The value $pK_A \approx 15{\cdot}3$ is presumed for the reaction $Z\text{-}IIIc(Z) \rightleftharpoons Z\text{-}IIIc(A) + H^+$ for the following reasons: *a*) the dependence of k_{obs}

on $[CH_3O^-]$ is linear up to the methoxide concentration $[CH_3O^-] = 8 \cdot 10^{-3}$ mol . l^{-1} (pH 14·8), hence the pK_A value of the above-mentioned reaction must be greater than 15; otherwise a decrease of the dependence slope would be observed; *b*) from the below-given calculation of k_{obs} it follows that the pK_A cannot be greater than 15·3.

For the acetate buffer $[CH_3COONa]/[CH_3COOH] = 100$ we compared the k value ($1{\cdot}1 \cdot 10^3$ l mol^{-1} s^{-1}) determined from the pH dependence of log k (Fig. 3) and Eq. (*10*) with that determined theoretically from Scheme 5 according to which

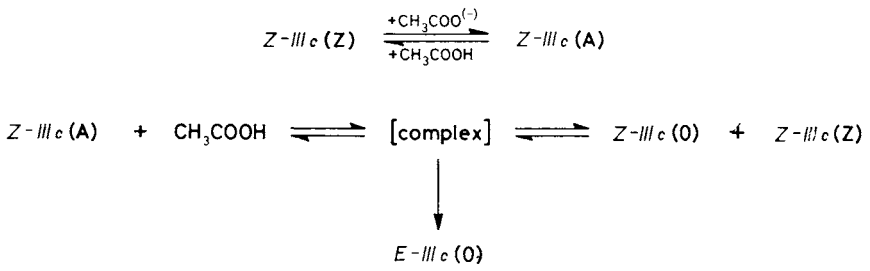


SCHEME 5

the reaction of *E-IIIc*(A) with acetic acid represents the rate-limiting step of the transformation. In the acetate buffer used the ratio is $[Z\text{-}IIIc(A)]/[Z\text{-}IIIc(Z)] \approx 10^{-4}$ (pH 11·25; $pK_A \approx 15{\cdot}3$). Even if we presume the equilibrium constant of the isomerization *Z-IIIc*(A) $\rightleftharpoons$ *E-IIIc*(A) to be $K_i = 10^{-3}$ and the rate constant of the reaction of *E-IIIc*(A) with acetic acid to have the value of $5 \cdot 10^9$ l mol^{-1} s^{-1} (which is the maximum value for a diffusion-controlled reaction of acetic acid with an amine[16]), we obtain the value of the rate constant $k_{calc} = 10^{-4} \cdot 10^{-3} \cdot 5 \cdot 10^9 \cdot 10^{-2}$ l mol^{-1} . . s^{-1} = 5 l mol^{-1} s^{-1} in a buffer with $[CH_3COOH] = 10^{-2}$ mol l^{-1} and $[CH_3COONa] = 1$ mol l^{-1}. The calculated value of the rate constant (k_{calc}) is by two orders of magnitude lower than that determined from kinetic measurements ($1{\cdot}1 \cdot 10^3$ l mol^{-1} s^{-1}), which means that the mechanism presented in Scheme 4 is not satisfactory. Also unsatisfactory is the analogous mechanism (*H*) involving the isomerization of zwitterion in the first step.

$$Z\text{-}IIIc(Z) \rightleftharpoons E\text{-}IIIc(Z) \rightleftharpoons E\text{-}IIIc(A) \rightarrow E\text{-}IIIc(0) \qquad (H)$$

From the value pK_A 15·3 and the ratio $[E\text{-}IIIc(0)]/[Z\text{-}IIIc(Z)] = 3{\cdot}4 \cdot 10^{-5}$ we obtain the value pK 10·8 for the acid-base reaction *E-IIIc*(0) $\rightleftharpoons$ *Z-IIIc*(A) + H^+. Hence the reaction of the dipolar ion *Z-IIIc*(Z) with acetic acid (pK_{A2} 9·25) is considerably advantageous thermodynamically, and it is possible to suggest that the cyclizable compound *E-IIIc*(0) is formed by a reaction pathway avoiding the thermodynamically unfavourable formation of the anion *E-IIIc*(A). In this mechanism, the protonation of the anion *Z-IIIc*(A) with acetic acid is connected with the isomerization as the rate-limiting step. The reaction course is represented in Scheme 6.



SCHEME 6

The anion *Z-IIIc*(A) produces a complex with acetic acid; the complex is either decomposed to the starting substances, or (depening on mutual orientation of the anion and acetic acid) reacts reversibly (to give *Z-IIIc*(0) and *Z-IIIc*(Z)) and irreversibly (to give *E-IIIc*(0)); the product *E-IIIc*(0) undergoes cyclization to spiro adduct *IIc*(A) in a subsequent reaction sequence. As the reaction *Z-IIIc*(A) + $CH_3COOH \rightarrow$ *E-IIIc*(0) + $CH_3COO^{(-)}$ is thermodynamically favourable ($\Delta pK \approx$ $\approx$ 1·6), the reverse decomposition of the complex is probably slower than the formation of the neutral intermediates *E-IIIc*(0) and *Z-IIIc*(0). For the rate of formation of *E-IIIc*(0) we can presume the value of (0·5 to 1) . 10^9 l mol^{-1} s^{-1}, hence k_{calc} = = $10^{-4} . 10^{-2} . (0{\cdot}5$ to $1) . 10^9 = (0{\cdot}5$ to $1) . 10^3$ l mol^{-1} s^{-1}. This value agrees well with the constant found (1·1 . 10^3 l mol^{-1} s^{-1}).

By analogy, the same mechanism with the same rate-limiting step also applies to the reactions carried out in the butylamine and piperidine buffers and methoxide solutions. In the triethylamine buffers, the rate constant k_{calc} is about four times as high as the value found experimentally. The reaction of the zwitterion *IIc*(Z) with a secondary and, still more, with a tertiary amine Eq. (*I*) is subject to steric hindrance[17].

$$IIc(Z) + R_3N \rightarrow IIc(A) + R_3\overset{(+)}{N}H \qquad (I)$$

In the case of the reaction with triethylamine, the retardation of the reaction (*I*) due to steric hindrance can be so great that this step becomes rate-limiting. This is also obvious from the kinetic experiments in which the dependence of k_{obs} on $[CH_3COO^{(-)}]$ was determined in the triethylamine–triethylammonium chloride buffers (Fig. 2). Slopes of the dependences have higher value at the acetate concentrations aproaching zero, especially so in the buffer of higher concentration. At the lowest acetate concentrations, the rate-limiting step predominantly consists in the reaction of the zwitterion *IIc*(Z) with acetate ion and triethylamine, because the formation of *E-IIIc*(0) is considerably accelerated by the triethylamine buffer (the rate constant calculated from the slope of the dependence of k_{obs} on

$[CH_3COO^{(-)}]$ at $[CH_3COO^{(-)}] \to 0$ in a buffer with the ratio $[(C_2H_5)_3N]/[(C_2H_5)_3NHCl] = 1$ and the concentration $[(C_2H_5)_3N] = 1{\cdot}5 \cdot 10^{-2}$ mol l^{-1} has a value above $1 \cdot 10^4$ l mol^{-1} s^{-1}). With increasing acetate concentration, the reaction of the zwitterion *IIc*(Z) with acetate ion is accelerated several times and becomes faster than the formation of *E-IIIc*(0), hence formation of *E-IIIc*(0) becomes the rate-limiting step. The rate constant calculated from the linear dependence of k_{obs} on $[CH_3COO^{(-)}]$ at higher concentrations of acetate is $(1{\cdot}2 \pm 0{\cdot}15) \cdot 10^3$ l mol^{-1} s^{-1}, which is – within experimental error – the same value as $1{\cdot}1 \cdot 10^3$ l mol^{-1} s^{-1} found for the given reaction pathway by the measurements in acetate buffers (Eqs (*8*) and (*10*)).

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